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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,288	11/28/2000	Dale B. Schenk	15270J-004765US	9431

20350 7590 07/12/2005

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EXAMINER	
TURNER, SHARON L	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 07/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,288	SCHENK ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *90-98 and 100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *90-98 and 100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5-23-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

Response to Amendment

1. The amendment filed 3-14-05 has been entered into the record and has been fully considered.

2. Claims 90-98 and 100 are pending.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

4. As a result of Applicant's amendment, all rejections not reiterated herein have been withdrawn.

5. Applicant's traversal of the species election requirement in the paper of 10-4-04 on the basis that the species are not mutually exclusive is found persuasive in that claims 90-97 specify that the amyloid deposits are comprised in a tissue sample. Accordingly the species election requirement is withdrawn and claims 50, 69-70 and 73-100 are under examination.

6. The Examiner further notes Applicant's previous traversal in which it is argued that a tissue is a species of biological entity physically associated with an antigen and that a tissue as an aggregation of similarly specialized cells united in performing a particular function.

Priority

7. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application);

the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). In particular, disclosure of the ex vivo screening assay as at pp. 96-100 of the specification is not noted within the 09/322,289 application. Accordingly, the effective filing date awarded instant claims is that of 5-26-00.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

9. Claims 90-92, 96-97 and 99 are rejected under 35 U.S.C. 102(e) as being anticipated by Solomon et al., WO 99/60024, 25 November 1999.

Solomon et al., teach methods for amyloid removal using anti-amyloid antibodies that enhance the cell-mediated immune response to deposits of amyloid and exploit the opsonizing effect of antibodies directed toward amyloid material, fibrils or its component parts both in vivo and in vitro. In particular, Figure 2A and 2B note in vitro adherence of human neutrophils (phagocytic cells bearing Fc receptors) after the amylid plaques were treated with anti-human IgLC monoclonal antibodies showing that the mouse mAb can bind to human amyloid as well as attract human neutrophils, see in particular pp. 18 and Figure 2. Thus, the reference teachings anticipate claims 50, 69-70, 73, 77-79, 81-84, 87-92, 96-97 and 99.

Applicant's argue in the response of 3-14-05 that Solomon is not directed to Amyloid beta deposits and that the reference does not evidence opsonizing or clearing effect.

Applicants arguments filed 3-14-05 have been fully considered but are not persuasive as to the amended claims newly directed to beta amyloid. In particular, Solomon is directed to treatment of beta amyloid accumulation as in Alzheimer's disease, directed to beta amyloid specific antibodies and to the opsonizing effect of such antibodies, see in particular pp. 1-3, Background, in particular p. 1, lines 21-26 with respect to "amyloidosis refer(ring) to the pathological deposition of proteins in the form of congophilic, green birefringent fibrils, when congo red-stained, either dispersed or in the form of localized amyloidomas, p. 3, line 4, with respect to "beta-amyloidosis

and for various therapeutic options", also p. 3, lines 13-15, "These methods exploit the opsonizing effect of mAbs directed toward the protein constituents of amyloid", p. 3, lines 21-22, "wherein binding of the polypeptide opsonizes the amyloid fibril,", p. 3, lines 24-26, "these antibodies have general anti-amyloid binding properties and provide an extrinsic opsonizing reagent that activates a patient's own cellular immune clearance mechanism." Page 12, lines 20-24 further delineate opsonization with respect to amyloid clearance. Thus, the reference teachings anticipate the claimed invention.

10. Claims 90-98 and 100 are rejected under 35 U.S.C. 102(e) as being anticipated by Vitek et al., US Patent No. 5,935,927 Aug. 10, 1999, filed Aug. 10, 1996 as further evidenced by evidenced by Benjamini et al., Immunology, 2nd, 1991, Wiley-Liss, Inc., New York, NY, pp. 136-138 and 143 and pp. 73-74, 372-373 and 400-401.

Vitek et al., teach compositions and methods for stimulating amyloid removal in amyloidogenic diseases using advanced glycosylation endproducts. In particular the method includes stimulating mechanisms of recognition and removal of AGE-amyloid in an animal to remove the amyloid plaques via scavenger systems such as phagocytic cells, macrophages and in neural tissue microglial cells, see in particular column 6, line 36-column 7, line 33. A particular embodiment of the invention includes wherein the therapeutic agents include antibodies to AGE-amyloid, in particular antibodies to AGE-beta amyloid, see in particular column 7, lines 11-16, column 12, lines 46-67, column 15, column 16, lines 44-52. In addition, Vitek teaches where the effectiveness of an AGE bearing targeting agent can be tested for efficacy, see in particular column 21-22,

paragraph spanning and column 24, lines 13-25, including the use of in vitro and in vivo assays, see in particular column 22, line 54-column 23, line 14. In particular, the method provides for combination of anti-AGE antibody, various antigens including beta amyloid antigen in vivo and in culture with phagocytic cells, including microglia with monitoring of the amount of AGE modified protein/antigen/biological entity (including AGE-beta amyloid) amongst samples and over time. The antibodies of Vitek include polyclonal and monoclonal antibodies, see in particular column 15, lines 26-58. Polyclonal antibodies are evidenced to bind to epitope within amino acid residues 1-7 of beta amyloid, see in particular pp. 96-100 of instant specification. The assays may be in vitro and in biological tissue, particularly where the tissue is from the brain of an animal having amyloid plaques or Alzheimer's pathology. Animal tissue comprises inflammatory cells and Alzheimer's plaques are considered nonmalignant abnormal cell growth. Moreover, the in vitro analysis may be in tissue sections viewed and fixed via microscopy on microscope slides as disclosed at column 32 Example 2. Such ADCC assays are widely accepted in the art as evidenced via Benjamini et al. In particular, Benjamini further evidences synthesis of the complement components via peripheral blood monocytes (PBMC) (inflammatory cells) as included in the cytotoxicity assay and Benjamini further notes the principles of the ADCC assay as noted for example at pp. 73-74, 372-373 and 400-401 including cytolysis mediated via antigen/antibody binding.

Applicants argue in the 3-14-05 response that Vitek does not disclose simultaneous presence of an antibody and phagocytic cells in an in vitro clearing reaction, and that Vitek does not disclose that the clearing reaction screens an antibody

for clearing activity. Appellants further argue that a specific exemplification of an ELISA for AGE-TF as a diagnostic reagent does not evidence that the antibody is present during the phagocytic step, asserting that the reference is deficient and that the burden is shifted to the PTO in view of *In re Piasecki.*

Applicants arguments filed 3-14-05 have been fully considered but are not persuasive. In contrast to Applicant's suggstion it is unclear how Vitek can be found deficient when the reference is directly on point to the mechanistic property of "Amyloid removal in amyloidogenic diseases," see in particular title, also claims, "A method for enhancing removal of amyloid from a peripheral tissue of a mammal afflicted with or developing a disease or disorder associated with amyhloidosis". The fact that this mechanistic property is provided by phagocytosis or opsonization is recognized via both Vitek, see for example column 6, lines 36-46 as previously cited, "The presence of high levels of AGE-amyloid polypeptides in amyloidogenic diseases indicates that the normal clearance mechanisms for such polypeptides are faulty. Therefore in a further aspect, the present invention provides compositions and methods for stimulating or inducing mechanisms of recognition and removal of AGE-amyloid in an animal, i.e., the invention contemplates activation of the scavenger system in an animal's body to remove the amyloid plaques. Such scavenger systems include the activity of phagocytic cells, e.g., macrophages and, in neural tissue microglial cells. " Ideally such agents constitute, "antagonists of advanced glycosylation, and include antibodies to AGEs, antibodies to AGE-amyloid polypeptide, in particular AGE-betaAP and AGE-amyloin, as well as other ligands that would bind and neutralize the foregoing antigens," see in particular column

7, lines 11-15. In contrast Vitek further notes the selection or screening of particular antibodies that comprise the removal/opsonizing/neutralizing effect mediated by phagocytes/macrophages/microglia, see in particular column 15, lines 8-26, also Treatment of Amyloidosis by Increasing AGE Clearance, columns 16-24. Thus, the references teachings in toto clearly evidence the recognition of the mechanism of the anti-AGE-beta amyloid antibodies as that of enhancing immune clearance or removal via phagocytosis or opsonization. The fact that the reference teaches the selection of suitable antibodies on such basis contradicts Applicants assertion that no screening method is provided. The fact that a single exemplary assay may or may not be conducted in the presence of a particular antibody cannot negate these broad teachings. Accordingly, rejection is maintained.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 90-98 and 100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vitek et al., US Patent No. 5,935,927 as further evidenced by evidenced by Benjamini et al., Immunology, 2nd, 1991, Wiley-Liss, Inc., New York, NY, pp. 136-138 and 143 and pp. 73-74, 372-373 and 400-401, Solomon et al., WO 99/60024, 25 November 1999, Herlyn et al., J. Immunol., 1979, 9:657-659, Jahrling et al., J. of Med. Virol., 12:1-16, 1983, Bellotti et al., Renal Failure 15(3):365-371, 1993

and Jorbeck et al., Infection & Immunity, 32(2):497-502, May 1981.

Vitek notes treatment in vivo of Alzheimers via administration of AGE amyloid antibodies and further notes in vitro assays for assessing plaque mediated clearance. In particular Vitek notes that "Further testing for clearance of the AGE-modified insoluble βAP (beta amyloid peptide) can be conducted by incubation with cultured phagocytic cells such as mouse peritoneal macrophages, elicited macrophages, the RAW 264.7 cell line, human peripheral monocytes or microglia or astroglia primary cells or cell lines," thereby implying an in vitro assay for assessment. Other in vitro assays for assessing antigen uptake via cytolytic or phagocytic cells are noted for example at columns 22-23. Vitek further notes assessment of such phagocytic activity in vivo, see in particular column 16-24.

However, Vitek does not specifically exemplify the noted phagocytic assay in vitro where the tissue is of Alzheimer's disease patient with antibody binding to epitope within residues 1-7.

Yet one of skill in the art is highly versed in assessing the ability of any antibody to mediate clearance of an antigen or cell via phagocytosis or cytolysis as evidenced via Benjamini, Solomon, Herlyn, Jahrling, Bellotti and Jorbeck both in vitro and in vivo as noted above. One of skill in the art would be motivated to assess such activity in vitro given the successful teachings of the AGE-beta amyloid antibody in vivo to mediate clearance of amyloid plaques as taught via Vitek. The reference provides guidance to the particular selection of antibodies reactive with beta amyloid, that are monoclonal or polyclonal, to the the proper tissues substrate comprised of amyloid plaques and to the

relevant phagocytic cells that have already shown to be effective in mediating opsonization and/or cell mediated cytotoxicity as directed via antibodies administered in vivo. The reference specifically suggests the performance of this same assay in vitro as noted for example at column 22-23. The performance of the assay in vitro provides for the superior advantages of an easily reproducible cell culture system that obviates the need for in vivo experimentation which is often unpredictable in nature, not easily reproduced, expensive and involves numerous ethical considerations particularly with the experimentation required in human cells and tissues. One of skill in the art would have an expectation of success utilizing such in vitro assays as ADCC and opsonization are art accepted principles and the performance of such assays either in vitro or in vivo are widely and routinely practiced in the art. Thus, the cumulative reference teachings render the claimed invention obvious to one of skill in the art.

Applicants argue in the response of 3-14-05 that the combination of references is unclear, case law with respect to broad teachings of multiple references, *In re Dembiczak* and that the claimed assay differs in that it is performed in vitro, that Viteks in vitro assays are not the same as claimed, that none of the references supplement as none are directed to in vitro clearance of amyloid beta. Applicants arguments with respect to the new limitations of a monoclonal antibody to residues 1-7 of beta-amyloid are deferred to the new rejections as necessitated by this amendment.

Applicants arguments have been fully considered but are not persuasive. It is not pertinent that no single claims are delineated as the references extend to those noted. Further, the multiple references are cumulative to the widely art accepted

principles and assays directed to assessing clearing acitivity of antibodies in the presence of noted antigenic samples, be they from in vivo or in vitro derived protocols. Accordingly, there is no deficiency and the case law of Dembiczak does not negate the specific teachings with respect to these art accepted principles. The applicability of an in vivo assay could be immediately applied in vitro once the antigen/antibody/clearing relationship is described as in Vitek. As previously noted, the assessment as in Vitek is modeled to the in vivo human condition of Alzheimer's disease and the tissues noted to be relevant to study for assessment of clearance are of patients afflicted with Alzheimer's disease. Accordingly the reference is not deficient with respect to clearance of amyloid beta from human Alzheimer's tissue, see in particular abstract, column 6, lines 36-46, as in diagnosis or assessment of treatment, see in particular columns 5-6 paragraphs spanning and extending through column 7, also Treatment of Neurodegenerative amyloidosis by inhibiting AGE, columns 12-16, and via increasing AGE clearance, columns 16-24 and Diagnostic Methods, column 24-27, measuring the amount or level of AGE-Beta AP (amyloid peptide) from biopsy or tissue sample, column 24, lines 46-54. Rejection therefore is maintained.

Rejections as Necessitated by Amendment

13. Claims 90-98 and 100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vitek et al., US Patent No. 5,935,927 as further evidenced by evidenced by Benjamini et al., Immunology, 2nd, 1991, Wiley-Liss, Inc., New York, NY, pp. 136-138 and 143 and pp. 73-74, 372-373 and 400-401, Solomon et al., WO 99/60024, 25 November 1999, Solomon et al., US 5,688,651, Frenkyl et al., J. of

Neuroimmunol., 88:85-90, 1998, Herlyn et al., J. Immunol., 1979, 9:657-659, Jahrling et al., J. of Med. Virol., 12:1-16, 1983, Bellotti et al., Renal Failure 15(3):365-371, 1993 and Jorbeck et al., Infection & Immunity, 32(2):497-502, May 1981.

Vitek, Benjamini and Solomon are as set forth above. Solomon further suggests use of the mAbs disclosed in Solomon US 5,688,651 noted to provide for solubilization of amyloid aggregates thereby further preventing protein aggregation, see in particular paragraph spanning pp. 2-3. While Solomon notes particular monoclonal antibodies reactive with beta amyloid and which promote solubilization or anti-aggregating properties they do not definitively establish the epitope to which the antibodies bind.

Frenkel et al., J. of Neuroimmunol., 88 :85-90, 1998 definitively establish the epitope specificity of the monoclonal antibodies noted to possess anti-aggregating or prevention of protein aggregation activity and which are the monoclonal antibodies suggested to be useful in the methods of Solomon US 5,688,651, further suggested to be used within the method of Solomon WO/9960024 for the purpose of promoting removal/opsonization/clearance of amyloid plaques as previously noted.

As similarly set forth above Herlyn, Jahrling, Bellotti and Jorbeck are further provided to establish the well known art recognized assays performed in vitro for assessing antibodies ability to clear/opsonize/remove antigenic protein formations via recognition of antibody binding to the antigen and clearance/opsonization/removal of the antigen/antibody complex via phagocytosis via macrophages, microglia or other phagocytic cells.

As particularly noted in Vitek, Solomon WO99/60024, Solomon 5,688,851, and Frenkel, the suitable tissue is of Alzheimer's patients for clearance and removal of Alzheimer's plaques. The in vitro procedure would be particularly recognized for testing procedures while the in vivo procedures would be particularly recognized for treatment, prevention and monitoring such parameters.

Solomon WO99/60024 motivates the selection of the monoclonal antibodies of Solomon 5,688,851 and Frenkel evidences that such monoclonal antibodies provide the requisite epitope specificity of Abeta residues 1-7. Thus, one of skill in the art would be motivated to use the in vitro assays of Solomon WO99/60024 or Vitek for assessing plaque mediated clearance (In particular Vitek notes that "Further testing for clearance of the AGE-modified insoluble βAP (beta amyloid peptide) can be conducted by incubation with cultured phagocytic cells such as mouse peritoneal macrophages, elicited macrophages, the RAW 264.7 cell line, human peripheral monocytes or microglia or astroglia primary cells or cell lines," thereby implying an in vitro assay for assessment. Other in vitro assays for assessing antigen uptake via cytolytic or phagocytic cells are noted for example at columns 22-23. Vitek further notes assessment of such phagocytic activity in vivo, see in particular column 16-24.) with the modification of utilization of mab of Solomon WO99/60024 assessed for opsonizing activity and further suggested for use with the mAb's of Solomon 5,688,851 evidenced by Frenkel to be specific to within epitope 1-7 of Abeta for screening that antibody for antivity in clearing beta amyloid depositions within the brain of Alzheiemr's patients. One of skill in the art would further expect success using this antibody in an in vitro

assay for assessment of the in vivo procedure given the high skill in the art of assessing such activity both in vitro and in vivo as in Solomon WO99/60024, 5,688,851, and Vitek. The artisan is further motivated to provide for the assessment in vitro such as to eliminate the ethical considerations regarding selection of such suitable antibody as effective in vivo, thereby substantiating the effectiveness of the procedure in vitro prior to in vivo administration. Thus, the cumulative reference teachings anticipate the claimed invention.

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

Sharon L. Turner, Ph.D.
June 13, 2005

SHARON TURNER, PH.D.
PRIMARY EXAMINER
6-13-05